Consommation et Corporations Canada
Consumer and Corporate Affairs Canada

Bureau des brevets
Patent Office

Ottawa, Canada
K1A 0C9

(21) (A1) 2,050,769

(22) 1991/09/06

(43) 1992/03/11

5,025,4/88

(51) INTL.CL.[5] C07D-403/06; C07D-403/14; C07D-401/14; C07D-405/14; C07D-409/14; C07D-233/70; C07F-009/645; C07F-009/651; A61K-031/41; A61K-031/44; A61K-031/505; A61K-031/675

(19) (CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Azacyclic Compounds

(72) Ostermayer, Franz - Switzerland ;
Herold, Peter - Switzerland ;
Fuhrer, Walter - Switzerland ;

(73) Ciba-Geigy AG - Switzerland ;

(30) (CH) 2927/90-7 1990/09/10

(57) 33 Claims

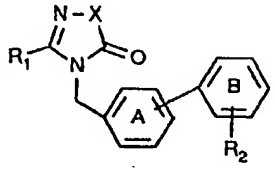
Canada

4-18240/A

Azacyclic compounds

Abstract

Azacyclic compounds of the formula



(I),

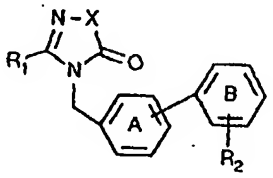
wherein X is the group of the formula $-C(R_3)R_4-[C(R_5)R_6]_p-[C(R_7)R_8]_q-$ (Ia) or the group of the formula $-N(R_9)-$ (Ib), R_1 is unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of hydroxy and halogen; cycloalkyl, cycloalkenyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, R_2 is carboxy, 1H-tetrazol-5-yl, SO_3H, PO_2H_2, PO_3H_2 or haloalkanesulfonylamino, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen, unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of halogen, free or etherified hydroxy, free or esterified or amidated carboxy and unsubstituted or substituted amino; free or esterified or amidated carboxy, cycloalkyl, cycloalkenyl, an aliphatic hydrocarbon radical interrupted by O, or an aromatic radical, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is a divalent aliphatic hydrocarbon radical and the variables of the other two pairs, independently of one another, are as defined above, R_9 is hydrogen or unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of free or etherified hydroxy and free or esterified or amidated carboxy, the indices p and q, independently of one another, are 0 or 1 and the rings A and B, independently of one another, are unsubstituted or substituted, and, if appropriate, the tautomers thereof, in each case in free form or in the form of salts,

can be prepared in a manner known per se and can be used, for example, as active ingredients in medicaments.

4-18240/A

Azacyclic compounds

The invention relates to azacyclic compounds of the formula



(I),

wherein X is the group of the formula $-C(R_3)R_4-[C(R_5)R_6]_p-[C(R_7)R_8]_q-$ (Ia) or the group of the formula $-N(R_9)-$ (Ib), R_1 is unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of hydroxy and halogen; cycloalkyl, cycloalkenyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, R_2 is carboxy, 1H-tetrazol-5-yl, SO_3H, PO_2H_2, PO_3H_2 or haloalkanesulfonylamino, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen, unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of halogen, free or etherified hydroxy, free or esterified or amidated carboxy and unsubstituted or substituted amino; free or esterified or amidated carboxy, cycloalkyl, cycloalkenyl, an aliphatic hydrocarbon radical interrupted by O, or an aromatic radical, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is a divalent aliphatic hydrocarbon radical and the variables of the other two pairs, independently of one another, are as defined above, R_9 is hydrogen or unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of free or etherified hydroxy and free or esterified or amidated carboxy, the indices p and q, independently of one another, are 0 or 1 and the rings A and B, independently of one another, are unsubstituted or substituted, in free form or in the form of salts, and, if appropriate, to the tautomers of those compounds, to the use of those compounds and tautomers, to a process for the preparation of those compounds and tautomers, and to pharmaceutical compositions comprising, in free form or in the form of a pharmaceutically acceptable salt, such a compound I or a tautomer thereof.

The compounds I may in some cases be in the form of proton tautomers. If, for example, X is a group -NH-, corresponding compounds I comprising the grouping -NH-C(=O)- may be in equilibrium with the tautomeric hydroxy derivatives, that is to say with the corresponding compounds having a grouping of the formula -N=C(OH)-. Accordingly, hereinbefore and hereinafter, any reference to the compounds I should be understood as including the corresponding tautomers as appropriate and expedient.

The compounds I may be in the form of salts, especially pharmaceutically acceptable salts. If the compounds I have at least one basic centre, they can form acid addition salts. The latter are formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, a phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as unsubstituted or substituted, for example halo-substituted, C_1-C_4alkanecarboxylic acids, for example acetic acid, saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, amino acids, for example aspartic or glutamic acid, or benzoic acid, or with organic sulfonic acids, such as unsubstituted or substituted, for example halo-substituted, C_1-C_4alkanesulfonic or arylsulfonic acids, for example methanesulfonic or p-toluenesulfonic acid. Corresponding acid addition salts can also be formed with a basic centre that may additionally be present. In addition, compounds I having at least one acidic group (for example COOH or 1H-tetrazol-5-yl) can form salts with bases. Suitable salts with bases are, for example, metal salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium or magnesium salts, or salts with ammonia or an organic amine, such as morpholine, thiomorpholine, piperidine, pyrrolidine, a mono-, di- or tri-lower alkylamine, for example ethyl-, tert-butyl-, diethyl-, diisopropyl-, triethyl-, tributyl- or dimethylpropyl-amine, or a mono-, di- or tri-hydroxy-lower alkylamine, for example mono-, di- or tri-ethanolamine. Furthermore, corresponding internal salts can be formed. The invention relates also to salts not suitable for pharmaceutical uses, which can be used, for example, for isolating and/or purifying free compounds I or their pharmaceutically acceptable salts.

The rings A and B form a biphenylyl radical, corresponding 4-biphenylyl being preferred and the radical R_2 preferably being located in a 2-position of ring B. The rings A and B, independently of one another, are unsubstituted or mono- or poly-substituted, for example di- or tri-substituted, it being possible for the substituents to be selected from the group

consisting of halogen, hydroxy, etherified hydroxy, amino, substituted amino, carboxy, esterified carboxy, amidated carboxy, lower alkyl, lower alkenyl, lower alkynyl, an aliphatic hydrocarbon radical interrupted by O, and trifluoromethyl.

Etherified hydroxy is lower alkoxy or lower alkenyloxy.

Esterified carboxy is carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl.

Amidated carboxy is carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene.

Substituted amino is amino that is mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene.

An aliphatic hydrocarbon radical interrupted by O is lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl or lower alkenyloxy-lower alkyl, -lower alkenyl or -lower alkynyl.

An aromatic radical is phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl.

A divalent aliphatic hydrocarbon radical is lower alkylene or lower alkenylene.

The aromatic radicals listed above, like the phenyl radicals in phenyl-substituted groups, for example in phenyl-lower alkyl groups, are, independently of one another, unsubstituted or mono- or poly-substituted, for example di- or tri-substituted, it being possible for the substituents to be selected from the group consisting of halogen, hydroxy, lower alkoxy, unsubstituted or substituted amino, free or esterified or amidated carboxy, lower alkyl, lower alkenyl, lower alkynyl and trifluoromethyl.

The general terms used hereinbefore and hereinafter, unless otherwise defined, have the following meanings.

The term "lower" denotes that corresponding groups and compounds comprise up to and including 7, preferably up to and including 4, carbon atoms.

Lower alkyl is C_1-C_7alkyl, that is to say, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl or a corresponding pentyl, hexyl or heptyl radical; C_1-C_4alkyl is preferred.

Lower alkenyl is C_3-C_7alkenyl and is, for example, propen-2-yl, allyl or but-1-en-3-yl, but-1-en-4-yl, but-2-en-1-yl or but-2-en-2-yl. C_3-C_5alkenyl is preferred.

Lower alkynyl is C_3-C_7alkynyl and is, for example, propargyl.

Lower alkylene is C_2-C_7alkylene, is straight-chained or branched, and is especially ethylene, prop-1,3-ylene, but-1,4-ylene, pent-1,5-ylene, prop-1,2-ylene, 2-methylprop-1,3-ylene or 2,2-dimethylprop-1,3-ylene. C_2-C_5alkylene is preferred.

Lower alkenylene is C_3-C_5alkenylene and is, for example, but-2-en-1,4-ylene.

Cycloalkyl is C_3-C_7cycloalkyl, that is to say, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Cyclopentyl and cyclohexyl are preferred.

Cycloalkenyl is C_3-C_7cycloalkenyl and is, for example, cyclopent-2-enyl or -3-enyl or cyclohex-2-enyl or -3-enyl.

Phenyl-lower alkyl is phenyl-C_1-C_4alkyl and is, for example, benzyl or 1- or 2-phenethyl, while phenyl-lower alkenyl and phenyl-lower alkynyl are phenyl-C_3-C_5alkenyl and -alkynyl, respectively, for example 3-phenylallyl or 3-phenylpropargyl.

Hydroxy-lower alkyl is hydroxy-C_1-C_4alkyl, such as hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl.

Lower alkoxy is C_1-C_7alkoxy, that is to say, methoxy, ethoxy, n-propoxy, isopropoxy,

n-butoxy, isobutoxy, sec-butoxy, tert-butoxy or corresponding pentyloxy, hexyloxy or heptyloxy. C_1-C_4alkoxy is preferred.

Lower alkenyloxy is C_3-C_7alkenyloxy and is, for example, allyloxy, but-2-en-1-yloxy or but-3-en-1-yloxy. C_3-C_5alkenyloxy is preferred.

Lower alkoxy-lower alkyl is C_1-C_4alkoxy-C_1-C_4alkyl, such as 2-methoxyethyl, 2-ethoxyethyl, 2-(n-propoxy)ethyl or ethoxymethyl.

Lower alkoxy-lower alkenyl and -lower alkynyl are C_1-C_4alkoxy-C_3-C_5-alkenyl and -alkynyl, respectively.

Lower alkenyloxy-lower alkyl is C_3-C_5alkenyloxy-C_1-C_4alkyl, such as 2-allyloxyethyl, and lower alkenyloxy-lower alkenyl and -lower alkynyl are C_3-C_5alkenyloxy-C_3-C_5-alkenyl and -alkynyl, respectively.

Lower alkyleneoxy-lower alkylene is C_2-C_4alkyleneoxy-C_2-C_4alkylene, for example ethyleneoxyethylene.

Halogen is especially halogen having an atomic number of up to and including 35, that is to say, fluorine, chlorine or bromine, and also includes iodine.

Haloalkanesulfonylamino is halo-C_1-C_7alkanesulfonylamino and is, for example, trifluoromethane-, difluoromethane-, 1,1,2-trifluoroethane- or heptafluoropropane-sulfonylamino. Halo-C_1-C_4alkanesulfonylamino is preferred.

Extensive pharmacological research has shown that the compounds I and their pharmaceutically acceptable salts have, for example, pronounced angiotensin II antagonistic properties.

Angiotensin II is known to have pronounced vasoconstrictive properties and, moreover, to stimulate aldosterone secretion, thus causing marked sodium/water retention. The result of angiotensin II activity manifests itself inter alia in an increase in blood pressure.

The importance of angiotensin II antagonists lies in the suppression, by competitive inhibition of the binding of angiotensin II to the receptors, of the effects of vaso-

constriction and of stimulation of aldosterone secretion produced by angiotensin II.

The angiotensin II antagonistic properties of the compounds I and their pharmaceutically acceptable salts can be detected in the angiotensin II binding test. In that test, smooth muscle cells from homogenised rat aorta are used. The solid centrifugate is suspended in 50 mM of tris buffer (pH 7.4) with the use of peptidase inhibitors. The samples are incubated for 60 minutes at 25°C with ^{125}I-angiotensin II (0.175 nM) and a varying concentration of angiotensin II or of test compound. The incubation is then terminated by the addition of ice-cold-phosphate-buffered saline and the reaction mixture is filtered through Whatman GF/F filters. The filters are counted using a gamma counter. The IC_{50} values are determined from the dose/activity curve. IC_{50} values of approximately 10 nM and above are found for the compounds I and their pharmaceutically acceptable salts.

Tests on isolated rings of rabbit aorta can be used to determine angiotensin II induced vasoconstriction. For that purpose, rings of aorta are dissected from each thorax and are fixed between 2 parallel clips at an initial tension of 2 g. The rings are then immersed in 20 ml of a tissue bath at 37°C and gassed with a mixture of 95 % O_2 and 5 % CO_2. The isometric reactions are measured. At 20-minute intervals the rings are stimulated alternately with 10 nM angiotensin II (Hypertensin - CIBA) and 5 nM noradrenalin chloride. The rings are then incubated with selected concentrations of the test compounds before being treated with the agonists. The data are analysed on a Buxco digital computer. The concentrations that effect 50 % inhibition of the initial control values are given as the IC_{50} values. IC_{50} values of approximately 5 nM and above are found for compounds I and their pharmaceutically acceptable salts.

The fact that the compounds I and their pharmaceutically acceptable salts are able to reduce high blood pressure induced by angiotensin II can be verified in the test model of the normotensive anaesthetised rat. After calibration of the preparations using 0.9 % NaCl (1 ml/kg i.v.) and noradrenalin (1 µg/kg i.v.) or angiotensin II (0.3 µg/kg i.v.), respectively, increasing doses (3-6) of the test compound are injected intravenously by means of bolus injection, whereupon after each dose angiotensin II or noradrenalin is administered at 5-minute intervals. The blood pressure is measured directly at the carotid and recorded in an on-line data-recording system (Buxco). The specificity of the angiotensin II antagonism is indicated by the selective inhibition of the pressure caused by angiotensin II but not of that caused by noradrenalin. In this test model, the compounds I and their pharmaceutically acceptable salts exhibit an inhibiting effect at a dose of

approximately 0.3 mg/kg i.v. and above.

The antihypertensive activity of the compounds I and their pharmaceutically acceptable salts can also be demonstrated in the test model of the renal hypertensive rat. High blood pressure is induced in male rats by constriction of a renal artery by the Goldblatt method. Doses of the test compound are administered to the rats using a stomach probe. Control animals receive an equivalent volume of solvent. Blood pressure and heartbeat are measured indirectly in conscious animals by the tail-clamping method of Gerold et al. [Helv. Physiol. Acta 24 (1966), 58] at intervals both before administration of the test compound or of the solvent and during the course of the experiments. The pronounced antihypertensive effect can be detected at a dose of approximately 30 mg/kg p.o. and above.

The compounds I and their pharmaceutically acceptable salts can accordingly be used, for example, as active ingredients in antihypertensive drugs which are used, for example, for the treatment of high blood pressure and of cardiac insufficiency. The invention thus relates also to the use of the compounds I and their pharmaceutically acceptable salts for the preparation of corresponding medicaments and for the therapeutic treatment of high blood pressure and of cardiac insufficiency. The preparation of the medicaments includes the commercial preparation of the active ingredients.

The invention relates especially to a compound of formula I wherein X is the group Ia or the group Ib, R_1 is unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of hydroxy and halogen; cycloalkyl, cycloalkenyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, R_2 is carboxy, 1H-tetrazol-5-yl, SO_3H, PO_2H_2, PO_3H_2 or haloalkanesulfonylamino, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen, unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of halogen, hydroxy, lower alkoxy, lower alkenyloxy, carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or to lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is di-substituted by lower alkylene or by lower

alkyleneoxy-lower alkylene; amino and amino that is mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene; or are carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or to lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is di-substituted by lower alkylene or by lower alkyleneoxy-lower alkylene; cycloalkyl, cycloalkenyl, lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, lower alkenyloxy-lower alkyl, -lower alkenyl or -lower alkynyl, phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is lower alkylene or lower alkenylene, and the variables of the other two pairs, independently of one another, are as defined immediately above, R_9 is hydrogen or unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of lower alkoxy, lower alkenyloxy, carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or to lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, and carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene, the indices p and q, independently of one another, are 0 or 1, and the rings A and B, independently of one another, are unsubstituted or mono- or poly-substituted, it being possible for the substituents to be selected from the group consisting of halogen, hydroxy, lower alkoxy, lower alkenyloxy, amino, amino mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene; carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or to lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is

disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene; and lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, -lower alkenyl and -lower alkynyl, lower alkenyloxy-lower alkyl, -lower alkenyl and -lower alkynyl and trifluoromethyl, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

The invention relates especially to a compound of formula I wherein X is the group Ia or the group Ib, R_1 is lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl or phenyl-lower alkyl, R_2 is carboxy, 1H-tetrazol-5-yl, SO_3H, PO_2H_2, PO_3H_2 or haloalkanesulfonylamino, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different lower alkyl substituents; cycloalkyl, lower alkoxy-lower alkyl, phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is lower alkylene or lower alkenylene and the variables of the other two pairs, independently of one another, are as defined immediately above, R_9 is hydrogen, lower alkyl, lower alkenyl or lower alkynyl, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B, independently of one another, are unsubstituted or mono- or poly-substituted, it being possible for the substituents to be selected from the group consisting of halogen, hydroxy, lower alkoxy, amino, amino mono- or di-substituted by identical or different substituents selected from lower alkyl and phenyl-lower alkyl, carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl and phenyl-lower alkyl, or is disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene; and lower alkyl and trifluoromethyl, and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

The invention relates more especially to a compound of formula I wherein X is the group Ia or the group Ib, R_1 is C_1-C_4alkyl, such as n-propyl or n-butyl, R_2 is carboxy or 1H-tetrazol-5-yl, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen or C_1-C_4alkyl, such as methyl or ethyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is C_2-C_5alkylene, such as but-1,4-ylene or pent-1,5-ylene, and the

variables of the other two pairs, independently of one another, are as defined immediately above, R_9 is hydrogen or C_1-C_4alkyl, such as methyl, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B are unsubstituted and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

The invention relates very especially to a compound of formula I wherein X is the group Ia or the group Ib, R_1 is C_1-C_4alkyl, such as n-propyl or n-butyl, R_2 is 1H-tetrazol-5-yl, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen or C_1-C_4alkyl, such as methyl or ethyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is C_2-C_5alkylene, such as but-1,4-ylene or pent-1,5-ylene, and the variables of the other two pairs are hydrogen, R_9 is hydrogen, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B are unsubstituted and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

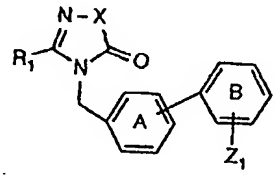
The invention relates especially to a compound of formula I wherein X is the group Ia, R_1 is C_1-C_4alkyl, such as n-propyl or n-butyl, R_2 is 1H-tetrazol-5-yl, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen or C_1-C_4alkyl, such as methyl or ethyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is C_2-C_5alkylene, such as but-1,4-ylene or pent-1,5-ylene and the variables of the other two pairs are hydrogen, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B are unsubstituted and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, in free form or in the form of a salt.

The invention relates most especially to a compound of formula I wherein X is the group Ia, R_1 is C_1-C_4alkyl, such as n-propyl or n-butyl, R_2 is 1H-tetrazol-5-yl, R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen or C_1-C_4alkyl, such as methyl or ethyl, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B are unsubstituted and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, in free form or in the form of a salt.

The invention relates specifically to the novel compounds of formula I mentioned in the Examples and, if appropriate, to tautomers thereof, in each case in free form or in the form of a salt.

The invention relates further to a process for the preparation of the compounds I and of their salts, which comprises, for example,

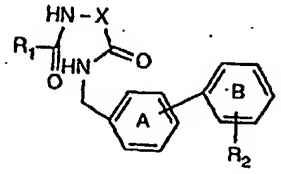
a) in a compound of the formula



(II),

wherein Z_1 is a radical that can be converted into R_2, or in a salt thereof, converting Z_1 into R_2, or

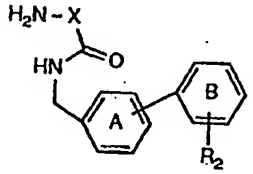
b) cyclising a compound of the formula



(III),

or a salt thereof, or

c) reacting a compound of the formula



(IV),

or a salt thereof, with a compound of the formula

R_1-$C(Z_2)(Z_3)Z_4$ (V),

wherein either Z_2 and Z_3 together are unmodified or functionally modified oxo and Z_4 is a nucleofugal leaving group, or Z_2, Z_3 and Z_4, independently of one another, are a nucleofugal leaving group, and in each case, if desired, converting a compound I obtainable in accordance with the process or in another manner, or a tautomer thereof, in each case in free form or in the form of a salt, into a different compound I or a tautomer thereof, separating a mixture of isomers obtainable in accordance with the process and isolating the desired isomer and/or converting a free compound I obtainable in accordance with the process, or a tautomer thereof, into a salt, or converting a salt of a compound I obtainable in accordance with the process, or of a tautomer thereof, into the free compound I or a tautomer thereof or into a different salt.

Salts of starting materials having at least one basic centre are corresponding acid addition salts, while salts of starting materials having at least one acidic group are salts with bases, in each case as described hereinbefore in connection with corresponding salts of compounds I.

The reactions described hereinbefore and hereinafter in the Variants are carried out in a manner known per se, for example in the absence or, customarily, in the presence of a suitable solvent or diluent or of a mixture thereof, and, as required, with cooling, at room temperature or with heating, for example in a temperature range of from approximately -80°C to the boiling temperature of the reaction medium, preferably from approximately -10° to approximately +200°C, and, if necessary, in a closed vessel, under pressure, in an inert gas atmosphere and/or under anhydrous conditions. Details of suitable reaction conditions are also to be found especially in the Examples.

Variant a):

Radicals Z_1 that can be converted into the variable R_2 are, for example, cyano, mercapto, halogen, the group $-N_2^+ A^-$, wherein A^- is an anion derived from an acid, amino, functional derivatives of COOH, SO_3H, PO_3H_2 and PO_2H_2, and protected 1H-tetrazol-5-yl.

Radicals Z_1 that can be converted into 1H-tetrazol-5-yl R_2 are, for example, cyano and protected 1H-tetrazol-5-yl.

For the preparation of compounds I wherein R_2 is 1H-tetrazol-5-yl, there is used as starting material, for example, starting material II wherein Z_1 is cyano, which is reacted, for example in an inert solvent, such as an aromatic or araliphatic hydrocarbon, for example in toluene or in a xylene, preferably while heating, with an azide, for example with HN_3 or, especially, a salt, such as an alkali metal salt, thereof, or with an organotin azide, such as tri-lower alkyltin azide or triaryltin azide. Preferred azides are, for example, sodium and potassium azide and tri-C_1-C_4alkyltin azide, for example trimethyl- or tributyl-tin azide, and triphenyltin azide.

Suitable protecting groups of protected 1H-tetrazol-5-yl are the protecting groups customarily used in tetrazole chemistry, especially triphenylmethyl, unsubstituted or substituted, for example nitro-substituted, benzyl, such as 4-nitrobenzyl, lower alkoxymethyl, such as methoxymethyl or ethoxymethyl, lower alkylthiomethyl, such as methylthiomethyl, and 2-cyanoethyl, also lower alkoxy-lower alkoxymethyl, such as 2-methoxyethoxymethyl, benzyloxymethyl and phenacyl. The removal of the protecting groups is effected in accordance with known methods. For example, triphenylmethyl is customarily removed by means of hydrolysis, especially in the presence of an acid, for example in the presence of hydrogen halide, advantageously in an inert solvent, such as a haloalkane or an ether, for example in dichloromethane or dioxane, and with heating, or by hydrogenolysis in the presence of a hydrogenation catalyst, 4-nitrobenzyl is removed, for example, by hydrogenolysis in the presence of a hydrogenation catalyst, methoxymethyl or ethoxymethyl is removed, for example, by treatment with a tri-lower alkyltin bromide, such as triethyl- or tributyl-tin bromide, methylthiomethyl is removed, for example, by treatment with trifluoroacetic acid, 2-cyanoethyl is removed, for example, by hydrolysis, for example with sodium hydroxide solution, 2-methoxyethoxymethyl is removed, for example, by hydrolysis, for example with hydrochloric acid, and benzyloxymethyl and phenacyl are removed, for example, by hydrogenolysis in the presence of a hydrogenation catalyst.

A radical Z_1 that can be converted into SO_3H R_2 is, for example, the mercapto group. Starting compounds II having such a group are oxidised, for example, by oxidising methods known per se to form compounds I wherein R_2 is SO_3H. Examples of suitable oxidising agents are inorganic peracids, such as peracids of mineral acids, for example periodic acid or persulfuric acid, organic peracids, such as percarboxylic or persulfonic acids, for example performic, peracetic, trifluoroperacetic or perbenzoic acid or p-toluenepersulfonic acid, or mixtures of hydrogen peroxide and acids, for example

mixtures of hydrogen peroxide and acetic acid. The oxidation is frequently carried out in the presence of suitable catalysts, there being mentioned as catalysts suitable acids, such as unsubstituted or substituted carboxylic acids, for example acetic acid or trifluoroacetic acid, or transition metal oxides, such as oxides of elements of subgroup VI, for example molybdenum or tungsten oxide. The oxidation is carried out under mild conditions, for example at temperatures of from approximately -50° to approximately +100°C.

A group that can be converted into PO_3H_2 R_2 is to be understood as being, for example, a group $-N_2^+ A^-$, A^- being an anion of an acid, such as a mineral acid. Corresponding diazonium compounds are, for example, reacted in a manner known per se with a phosphorus(III) halide, such as PCl_3 or PBr_3, and worked up by hydrolysis, compounds I wherein R_2 is PO_3H_2 being obtainable.

Compounds I wherein R_2 is PO_2H_2 are obtained, for example, by converting Z_1 in a compound II wherein Z_1 is a functional derivative of PO_2H_2 into PO_2H_2 in a customary manner.

A suitable radical Z_1 that can be converted into haloalkanesulfonylamino R_2 is, for example, amino. For the preparation of compounds I wherein R_2 is haloalkanesulfonylamino, for example corresponding anilines are reacted with a haloalkanesulfonic acid that has been reactively esterified in customary manner, the reaction being carried out, if desired, in the presence of a base. The preferred reactively esterified haloalkanesulfonic acid is the corresponding halide, such as the chloride or bromide.

A radical Z_1 that can be converted into COOH R_2 is, for example, functionally modified carboxy, such as cyano, esterified or amidated carboxy, hydroxymethyl or formyl.

Esterified carboxy is, for example, carboxy esterified by an unsubstituted or substituted aliphatic, cycloaliphatic or aromatic alcohol. An aliphatic alcohol is, for example, a lower alkanol, such as methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol or tert-butanol, while a suitable cycloaliphatic alcohol is, for example, a 3- to 8-membered cycloalkanol, such as cyclo-pentanol, -hexanol or -heptanol. An aromatic alcohol is, for example, a phenol or a heterocyclic alcohol, each of which may be substituted, especially hydroxypyridine, for example 2-, 3- or 4-hydroxypyridine.

Amidated carboxy is, for example, carbamoyl, or carbamoyl that is monosubstituted by

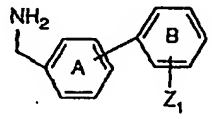
hydroxy, amino or by unsubstituted or substituted phenyl, mono- or di-substituted by lower alkyl, or disubstituted by 4- to 7-membered alkylene or by 3-aza-, 3-lower alkylaza-, 3-oxa- or 3-thia-alkylene. Examples that may be mentioned are carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, such as N-methyl-, N-ethyl-, N,N-dimethyl-, N,N-diethyl- and N,N-dipropyl-carbamoyl, pyrrolidino- and piperidino-carbonyl, morpholino-, piperazino-, 4-methylpiperazino- and thiomorpholino-carbonyl, anilinocarbonyl and anilinocarbonyl substituted by lower alkyl, lower alkoxy and/or by halogen.

Preferred functionally modified carboxy is lower alkoxycarbonyl, such as methoxy- or ethoxy-carbonyl, and cyano.

Compounds I wherein R_2 is carboxy can be prepared, for example, starting from compounds II wherein Z_1 is cyano or esterified or amidated carboxy, by means of hydrolysis, especially in the presence of a base, or, starting from compounds II wherein Z_1 is hydroxymethyl or formyl, by means of oxidation. The oxidation is carried out, for example, in an inert solvent, such as a lower alkanecarboxylic acid, for example acetic acid, a ketone, for example acetone, an ether, for example tetrahydrofuran, a heterocyclic aromatic compound, for example pyridine, or in water, or in a mixture thereof, if necessary while cooling or heating, for example in a temperature range of from approximately 0° to approximately +150°C. Examples of suitable oxidising agents are oxidising transition metal compounds, especially those having elements of subgroup I, VI or VII. Examples that may be mentioned are: silver compounds, such as silver nitrate, oxide and picolinate, chromium compounds, such as chromium trioxide and potassium dichromate, and manganese compounds, such as potassium, tetrabutylammonium permanganate and benzyltriethylammonium permanganate. Further examples of oxidising agents are suitable compounds having elements of main group IV, such as lead dioxide, or halo-oxygen compounds, such as sodium iodate or potassium periodate.

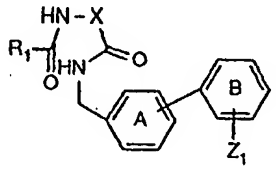
The starting material II can be obtained by analogy with known methods, for example by reacting an acid of the formula H_2N-X-COOH (IIa) or an ester of the formula H_2N-X-COOE (IIa'; -COOE = an ester group, for example lower alkoxycarbonyl, such as methoxy- or ethoxy-carbonyl) in the presence of a base with a compound of the formula R_1-C(=O)-Z_5 (IIb; Z_5 = a nucleofugal leaving group, for example halogen, such as chlorine), if desired hydrolysing the ester group -COOE in the reaction product, reacting the resulting acid of the formula R_1-C(=O)-NH-X-COOH (IIc), if desired after conversion into a reactive acid derivative, for example after reaction with N-hydroxysuccinimide, in

the presence of a water-binding agent, such as a carbodiimide, for example in the presence of N,N'-dicyclohexylcarbodiimide, advantageously in an inert solvent, for example in an N,N-di-lower alkyl-lower alkanoic acid amide, such as in N,N-dimethylformamide, with a compound of the formula



(IId)

to form a compound of the formula

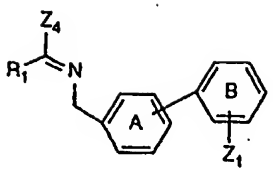


(IIe)

which is then cyclised, for example in the presence of an acid, such as an organic sulfonic acid, for example in the presence of p-toluenesulfonic acid, and if desired while heating, to form a compound II.

In accordance with a preferred embodiment of Variant a) it is possible, without isolating the compounds II, to obtain compounds I wherein R_2 is 1H-tetrazol-5-yl directly from compounds IIe wherein Z_1 is cyano by reacting corresponding compounds IIe, for example in an inert solvent, such as an aromatic or araliphatic hydrocarbon, for example in toluene or a xylene, preferably while heating, with an azide, for example with HN_3 or, especially, a salt, such as an alkali metal salt, thereof, or with an organotin azide, such as tri-lower alkyl- or triaryl-tin azide. The azides mentioned above are preferred.

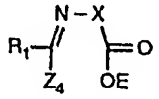
The starting material II is also obtainable by reacting a compound V with a compound IId, for example in an inert solvent, such as an aromatic or araliphatic hydrocarbon, for example in toluene or a xylene, and preferably while heating, and reacting the resulting compound of the formula



(IIf)

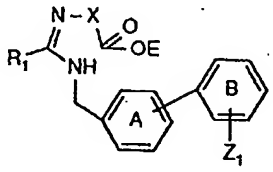
with a compound IIa', for example in an inert solvent, such as an aromatic or araliphatic hydrocarbon, for example in toluene or a xylene, and preferably while heating and if desired in the presence of a basic agent, such as in the presence of pyridine or triethylamine.

Furthermore, the starting material II is also obtainable by reacting a compound V with a compound IIa', for example in an inert solvent, such as toluene or a xylene, and if desired in the presence of a basic agent, such as in the presence of pyridine or triethylamine, reacting the resulting compound of the formula



(IIn)

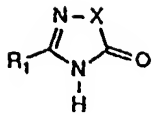
with a compound IId, for example in an inert solvent, such as toluene or a xylene, and if desired in the presence of a basic agent, such as in the presence of pyridine or triethylamine, to form a compound of the formula IIm



(IIm)

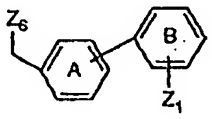
which is then cyclised to form a compound II, for example in an inert solvent, such as an aromatic or araliphatic hydrocarbon, for example in toluene or a xylene, and preferably while heating.

Finally, the starting material II is also obtainable by reacting a compound of the formula



(IIh)

with a compound of the formula



(IIi),

wherein Z_6 is a nucleofugal leaving group, for example halogen, such as chlorine or bromine, for example in an inert solvent, such as an N,N-di-lower alkyl-lower alkanoic acid amide, for example in N,N-dimethylformamide, and preferably in the presence of a basic agent, such as an alkali metal hydride, for example in the presence of sodium or potassium hydride.

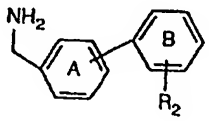
A compound IIh is obtained, for example, by reacting a compound of the formula H_2N-X-C(=O)-NH_2 (IIg) with a compound V, for example in an inert solvent, such as toluene or a xylene, and preferably while heating, and if desired in the presence of a basic agent, such as in the presence of pyridine or triethylamine, or by reacting a compound of the formula R_1-C(=NH)-Z_7 (IIj; Z_7 = a nucleofugal leaving group, preferably lower alkoxy, such as methoxy or ethoxy) with a compound IIa', for example in an inert solvent, such as an aromatic or araliphatic hydrocarbon, for example in toluene or a xylene, and preferably while heating, and if desired in the presence of a basic agent, such as in the presence of pyridine or triethylamine, or by reacting a compound of the formula R_1-C(=NH)-NH_2 (IIk) with a compound IIa' or, for the preparation of compounds IIh wherein X is a group of the formula -C(R_3)R_4-CH(R_5)- (Ia'), with a compound of the formula (R_3)R_4C=C(R_5)-C(=O)-OE (IIo; -COOE = an ester group, for example lower alkoxycarbonyl, such as methoxy- or ethoxy-carbonyl), if desired in an inert solvent, such as toluene or a xylene, and if desired while heating.

Variant b):

The cyclisation is effected in a manner known per se, for example in an inert solvent, such as an aromatic or araliphatic hydrocarbon, for example in toluene or a xylene, preferably while heating, and if desired in the presence of a basic agent, such as in the presence of pyridine or triethylamine, or of an acidic agent, for example in the presence of an acid,

such as a mineral acid or an organic carboxylic or sulfonic acid, for example in the presence of a hydrohalic acid, such as hydrochloric acid, or of acetic acid or p-toluene-sulfonic acid.

The starting material III can be prepared in a manner known per se, for example by reacting an acid of the formula R_1-C(=O)-NH-X-COOH (IIc), if desired after conversion into a reactive acid derivative, for example after reaction with N-hydroxysuccinimide, in the presence of a water-binding agent, such as a carbodiimide, for example in the presence of N,N'-dicyclohexylcarbodiimide, advantageously in an inert solvent, for example in an N,N-di-lower alkyl-lower alkanoic acid amide, such as N,N-dimethylformamide, with a compound of the formula



(IIIa),

it being possible for compounds IIc to be obtained, for example, as described in Variant a).

Variant c):

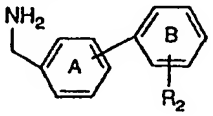
Unmodified or functionally modified oxo (Z_2 and Z_3 together) is, for example, oxo, thioxo or unsubstituted or substituted imino, such as imino, N-lower alkylimino, N-benzoylimino or N-lower alkanesulfonylimino.

A nucleofugal leaving group Z_2 or Z_3 or Z_4 is, for example, hydroxy, lower alkoxy, such as methoxy or ethoxy, lower alkylthio, such as methylthio, unsubstituted or substituted amino, such as amino, N-lower alkylamino or N,N-di-lower alkylamino, or sulfonyloxy, such as unsubstituted or halogenated lower alkanesulfonyloxy or unsubstituted or substituted benzenesulfonyloxy, such as methane-, ethane-, trifluoromethane-, benzene- or p-toluene-sulfonyloxy. Preferred are compounds V wherein Z_2, Z_3 and Z_4 are lower alkoxy, such as methoxy or ethoxy, that is to say, R_1-substituted orthoesters.

The reaction of a compound IV with a compound V is effected by analogy with known methods under the customary reaction conditions, for example in an inert solvent, such as an aromatic or araliphatic hydrocarbon, for example in toluene or a xylene, at room temperature or while heating and if desired in the presence of an acidic agent, for example in the presence of an acid, such as a mineral acid or an organic carboxylic acid or sulfonic

acid, for example in the presence of a hydrohalic acid, such as hydrochloric acid, or of acetic acid or p-toluenesulfonic acid.

The starting material IV can be obtained in a manner known per se, for example by reacting an acid of the formula H_2N-X-C(=O)-OH (IIa), if desired after conversion into a reactive acid derivative, for example after reaction with N-hydroxysuccinimide, in the presence of a water-binding agent, such as a carbodiimide, for example in the presence of N,N'-dicyclohexylcarbodiimide, advantageously in an inert solvent, for example in an N,N-di-lower alkyl-lower alkanoic acid amide, such as N,N-dimethylformamide, with a compound of the formula



(IIIa).

The starting material V is known or can be prepared by analogy with known methods.

A compound I obtainable in accordance with the process or in another manner or a tautomer thereof can be converted in a manner known per se into a different compound I or a tautomer thereof.

For example, a compound I having a hydroxy group can be etherified by methods known per se. The etherification can be carried out, for example, with an alcohol, such as a lower alkanol, or a reactive ester thereof. Examples of suitable reactive esters of the desired alcohols are those with strong inorganic or organic acids, such as corresponding halides, sulfates, lower alkanesulfonates or unsubstituted or substituted benzenesulfonates, for example chlorides, bromides, iodides or methane-, benzene- or p-toluene-sulfonates. The etherification can be carried out, for example, in the presence of a base, for example an alkali metal hydride, hydroxide or carbonate, or of a basic amine. Conversely, corresponding ethers, such as lower alkoxy compounds, can be cleaved, for example, by means of strong acids, such as mineral acids, for example hydrobromic or hydriodic acid, which may advantageously be in the form of pyridinium halides, or by means of Lewis acids, for example halides of elements of main group III or the corresponding subgroups. These reactions can, if necessary, be carried out while cooling or heating, for example in a temperature range of from approximately -20° to approximately +100°C, in the presence or absence of a solvent or diluent, under an inert gas and/or under pressure and if desired in a closed vessel.

If one of the variables comprises amino, corresponding compounds I can be N-(ar)alkylated in a manner known per se; carbamoyl or carbamoyl-containing radicals can likewise be N-(ar)alkylated. The (ar)alkylation is carried out, for example, using an (aryl-)C_1-C_7alkyl halide, for example bromide or iodide, an (aryl-)C_1-C_7alkanesulfonate, for example methanesulfonate or p-toluenesulfonate, or a di-C_1-C_7alkylsulfate, for example dimethylsulfate, preferably under basic conditions, such as in the presence of sodium hydroxide solution or potassium hydroxide solution, and advantageously in the presence of a phase-transfer catalyst, such as tetrabutylammonium bromide or benzyltrimethylammonium chloride, although more strongly basic condensation agents, such as alkali metal amides, hydrides or alcoholates, for example sodium amide, sodium hydride or sodium ethanolate, may be necessary.

In compounds I having as substituent an esterified or amidated carboxy group, such a group can be converted into a free carboxy group, for example by means of hydrolysis, for example in the presence of a basic agent or an acidic agent, such as a mineral acid.

Furthermore, in compounds I having as substituent a carboxy group (especially in the case where R_2 is other than carboxy), that group can be converted into an esterified carboxy group, for example by treatment with an alcohol, such as a lower alkanol, in the presence of a suitable esterifying agent, such as an acidic reagent, for example an inorganic or organic acid or a Lewis acid, for example zinc chloride, or of a water-binding condensation agent, for example a carbodiimide, such as N,N'-dicyclohexylcarbodiimide, or by treatment with a diazo reagent, such as a diazo-lower alkane, for example diazomethane. The esterified carboxy group can also be obtained by treating compounds I wherein the carboxy group is in free form or in the form of a salt, such as an ammonium or metal salt, for example an alkali metal salt, such as a sodium or potassium salt, with a C_1-C_7alkyl halide, for example methyl or ethyl bromide or iodide, or an organic sulfonic acid ester, such as a corresponding C_1-C_7alkyl ester, for example methanesulfonic acid or p-toluenesulfonic acid methyl ester or ethyl ester.

Compounds I having as substituent an esterified carboxy group can be converted into other ester compounds I by means of transesterification, for example by treatment with an alcohol, customarily with an alcohol that is higher than the alcohol corresponding to the esterified carboxy group in the starting material, in the presence of a suitable transesterifying agent, such as a basic agent, for example an alkali metal C_1-C_7alkanoate, an alkali

metal C_1-C_7alkanolate or an alkali metal cyanide, such as sodium acetate, sodium methanolate, sodium ethanolate, sodium tert-butanolate or sodium cyanide, or of a suitable acidic agent, if desired with the removal of the resulting alcohol, for example by means of distillation. It is also possible to use as starting material corresponding, so-called activated esters I having as substituent an activated esterified carboxy group (see below) and to convert the latter into a different ester by treatment with a C_1-C_7alkanol.

In compounds I having a carboxy group as substituent, it is also possible first to convert that group into a reactive derivative, such as an anhydride (including a mixed anhydride), an acid halide, for example an acid chloride (for example by treatment with a thionyl halide, for example thionyl chloride), an anhydride with a formic acid ester, for example a formic acid C_1-C_7alkyl ester (for example by treatment of a salt, such as an ammonium salt or an alkali metal salt, with a haloformic, such as chloroformic, acid ester, such as C_1-C_7alkyl ester), or an activated ester, such as cyanomethyl ester, nitrophenyl ester, for example 4-nitrophenyl ester, or a polyhalophenyl ester, for example pentachlorophenyl ester (for example by treatment with a corresponding hydroxy compound in the presence of a suitable condensation agent, such as N,N'-dicyclohexylcarbodiimide) and then to react such a reactive derivative with an amine to obtain amide compounds I having an amidated carboxy group as substituent. The amide compounds I can be obtained directly or by way of intermediate compounds; thus it is possible first to react, for example, an activated ester, such as a 4-nitrophenyl ester, of a compound I having a carboxy group with a 1-unsubstituted imidazole and to react the resulting 1-imidazolylcarbonyl compound with an amine. It is, however, also possible to react other, non-activated esters, such as C_1-C_7alkyl esters, of compounds I with amines.

If an aromatic ring has as substituent a hydrogen atom, the latter can be replaced by a halogen atom in customary manner using a halogenating agent, for example by bromine using bromine, hypobromic acid, an acyl hypobromite or another organic bromine compound, for example N-bromosuccinimide, N-bromoacetamide, N-bromophthalimide, pyridinium perbromide, dioxane dibromide, 1,3-dibromo-5,5-dimethylhydantoin or 2,4,4,6-tetrabromo-2,5-cyclohexanedien-1-one, or by chlorine using elemental chlorine, for example in a halogenated hydrocarbon, such as chloroform, and while cooling, for example to approximately -10°C.

If an aromatic ring comprises an amino group, the amino group can be diazotised in customary manner, for example by treatment with a nitrite, for example sodium nitrite, in

the presence of a suitable protonic acid, for example a mineral acid, the reaction temperature advantageously being maintained at below approximately 5°C. The diazonium group so obtainable, which is in salt form, can be substituted in accordance with customary methods, for example as follows: by the hydroxy group by analogy with the boiling down of phenol in the presence of water; by an alkoxy group by treatment with a corresponding alcohol, the supply of energy being required; by the fluorine atom by analogy with the Schiemann reaction in the thermal decomposition of corresponding diazonium tetrafluoroborates; or by chlorine, bromine, iodine or the cyano group by analogy with the Sandmeyer reaction by reaction with corresponding Cu(I) salts, first of all with cooling, for example to below approximately 5°C, and then with heating, for example to from approximately 60° to approximately 150°C.

If the compounds I comprise unsaturated radicals, such as lower alkenyl or lower alkynyl groupings, those groupings can be converted in a manner known per se into saturated radicals. For example the hydrogenation of multiple bonds is effected by catalytic hydrogenation in the presence of hydrogenation catalysts, there being suitable for the purpose, for example, nickels, such as Raney nickel, and noble metals and their derivatives, for example oxides, such as palladium or platinum oxide, which may, if desired, have been applied to carrier materials, for example to carbon or calcium carbonate. The hydrogenation is preferably carried out at pressures of from approximately 1 to approximately 100 atm and at temperatures of from approximately -80° to approximately +200°C, especially from room temperature to approximately 100°C. The reaction is advantageously carried out in a solvent, such as water, a lower alkanol, for example ethanol, isopropanol or n-butanol, an ether, for example dioxane, or a lower alkanecarboxylic acid, for example acetic acid.

The invention relates especially to the processes described in the Examples.

Salts of compounds I can be prepared in a manner known per se. For example acid addition salts of compounds I are obtained by treatment with a suitable acid or a suitable ion-exchange reagent. Salts of compounds I can be converted into the free compounds I in customary manner, acid addition salts for example by treatment with a suitable basic agent or a suitable ion-exchange reagent.

Salts of compounds I can be converted into other salts of compounds I in a manner known per se.

Depending upon the procedure and the reaction conditions, compounds I having salt-forming, especially basic, properties, can be obtained in free form or in the form of salts.

In view of the close relationship between the compounds I in free form and in the form of their salts, hereinbefore and hereinafter any reference to the free compounds I or their salts should be understood as including the corresponding salts or free compounds I, respectively, as appropriate and expedient.

The compounds I, including the salts of salt-forming compounds, may also be obtained in the form of their hydrates and/or may include other solvents, for example solvents used for crystallisation.

Depending upon the starting materials and procedures chosen, the compounds I and their salts may be in the form of one of the possible isomers or in the form of a mixture thereof, for example, depending on the number and the absolute and relative configuration of the asymmetric carbon atoms, in the form of pure isomers, such as antipodes and/or diastereoisomers, or in the form of mixtures of isomers, such as mixtures of enantiomers, for example racemates, mixtures of diastereoisomers or mixtures of racemates.

Mixtures of diastereoisomers and mixtures of racemates that are obtained can be separated in known manner into the pure diastereoisomers or racemates on the basis of the physicochemical differences between the constituents, for example by fractional crystallisation. Mixtures of enantiomers that are obtained, such as racemates, can be separated in accordance with known methods into the optical antipodes, for example by recrystallisation from an optically active solvent, chromatography on chiral adsorbents, with the aid of suitable microorganisms, by cleavage with specific immobilised enzymes, by the formation of inclusion compounds, for example using chiral crown ethers, only one enantiomer being complexed, or by conversion into diastereoisomeric salts, for example by reaction of a basic end product racemate with an optically active acid, such as carboxylic acid, for example tartaric acid or malic acid, or sulfonic acid, for example camphorsulfonic acid, and separation of the mixture of diastereoisomers obtained in that manner, for example on the basis of their different solubilities, into the diastereoisomers from which the desired enantiomer can be freed by the action of suitable agents. Advantageously, the more active enantiomer is isolated.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out, or in which a starting material is used in the form of a derivative or salt and/or racemates or antipodes thereof or, especially, is formed under the reaction conditions.

The starting materials and intermediates used in the process of the present invention are preferably those which result in the compounds I described at the beginning as being especially valuable. The invention relates also to novel starting materials and intermediates for the preparation of compounds I, their use and a method for their preparation, the variables R_1, R_2 and X and the rings A and B being as defined for the compounds I.

The compounds I and their pharmaceutically acceptable salts can be used, preferably in the form of pharmaceutically acceptable preparations, in a method for the prophylactic and/or therapeutic treatment of the animal or human body, especially as antihypertensive drugs.

The invention therefore relates also to pharmaceutical compositions that comprise as active ingredient a compound I in free form or in the form of a pharmaceutically acceptable salt, and to a process for the preparation thereof. Such pharmaceutical compositions are for enteral, such as oral, and rectal or parenteral administration to warm-blooded animals, the compositions comprising the pharmacological active ingredient alone or together with customary pharmaceutical excipients. The pharmaceutical compositions comprise, for example, from approximately 0.1 % to 100 %, preferably from approximately 1 % to approximately 60 %, active ingredient. Pharmaceutical compositions for enteral and parenteral administration are, for example, those in unit dose form, such as dragées, tablets, capsules or suppositories, and also ampoules. They are manufactured in a manner known per se, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture, and processing the mixture or granules, if desired or necessary, after the addition of suitable excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate or calcium hydrogen phosphate, also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and if desired disintegrators, such as the above-mentioned starches, also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar or alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable non-enteric or enteric coatings, there being used, inter alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures, or, for the production of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Colourings or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further orally administrable pharmaceutical compositions are dry-filled capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers may likewise be added.

There come into consideration as rectally administrable pharmaceutical compositions, for example, suppositories that consist of a combination of the active ingredient and a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules that contain a combination of the active ingredient and a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

Suitable for parenteral administration are especially aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, and also

suspensions of the active ingredient, such as corresponding oily injection suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions that comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and, optionally, also stabilisers.

The dose of the active ingredient may depend upon various factors, such as method of administration, the species of warm-blooded animal, age and/or individual condition. In normal cases, the approximate daily dose for a patient weighing about 75 kg is estimated to be, in the case of oral administration, from approximately 10 mg to approximately 250 mg.

The following Examples illustrate the invention described above but are not intended to limit the scope thereof in any way. Temperatures are given in degrees Celsius.

Example 1: While stirring, a solution of 7.55 g (20 mmol) of 2-methyl-2-pentanoylamino-propionic acid N-(2'-cyanobiphenyl-4-ylmethyl)amide and 10.6 g (32 mmol) of tributyltin azide in 100 ml of o-xylene is heated under reflux for 40 hours. After cooling, 80 ml of 1N sodium hydroxide solution are added to the reaction mixture and the mixture is stirred for from 2 to 3 hours. The aqueous phase is separated off and the pH is brought to from 3 to 4 with 1N hydrochloric acid. The oil that separates is extracted with ethyl acetate and the resulting crude product is purified by flash chromatography (silica gel 60, 40-63 µm, toluene/isopropanol/glacial acetic acid = 170/30/2). The fractions having an R_f value of 0.29 in that system are combined and concentrated by evaporation and the residue is recrystallised from isopropanol, yielding 2-(n-butyl)-4,4-dimethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole having a melting point of 181-182°.

The starting material can be prepared, for example, as follows:
a) 2-amino-2-methylpropionic acid methyl ester hydrochloride and pentanoyl chloride are reacted in dioxane/Hünig base to form 2-methyl-2-pentanoylaminopropionic acid methyl ester. The latter is hydrolysed in its crude form in dioxane with 2N sodium hydroxide solution to form 2-methyl-2-pentanoylaminopropionic acid [m.p.: 144-148° (from ethyl acetate)].

b) 7.5 g (63 mmol) of N-hydroxysuccinimide and 9.6 g (47 mmol) of N,N'-dicyclohexyl-

carbodiimide are added to a solution of 7.5 g (40 mmol) of 2-methyl-2-pentanoylamino-propionic acid in 100 ml of N,N-dimethylformamide. The mixture is stirred for 15 minutes, then a solution of 8.3 g (40 mmol) of 4-aminomethyl-2'-cyanobiphenyl in 20 ml of N,N-dimethylformamide is added and the reaction mixture is then stirred for 24 hours at room temperature. The resulting precipitate is filtered off and the filtrate is concentrated by evaporation in vacuo. The resulting residue is partitioned between ethyl acetate and 2N sodium hydroxide solution and the organic phase is separated off, dried and concentrated by evaporation, yielding 2-methyl-2-pentanoylaminopropionic acid N-(2'-cyanobiphenyl-4-ylmethyl)amide in the form of a yellow oil that gradually solidifies to form crystals and can be used further in its crude form.

Example 2: 5 ml of 2N hydrochloric acid are added to a solution of 1.3 g (2 mmol) of 2-(n-butyl)-4,4-dimethyl-5-oxo-1-[2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole in 30 ml of dioxane and the mixture is heated for from 2 to 3 hours at 80°. The dioxane is evaporated off and the residue is partitioned between 10 ml of 2N sodium hydroxide solution and 30 ml of ethyl acetate. Working up of the sodium hydroxide solution extract analogously to Example 1 yields 2-(n-butyl)-4,4-dimethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole [m.p.: 181-182° (from isopropanol)].

The starting material can be obtained, for example, as follows:
a) 1-ethoxy-1-iminopentane and 2-amino-2-methylpropionic acid ethyl ester are reacted to form 2-(n-butyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazole, which is obtained in the form of an oil [R_f = 0.33 (toluene/isopropanol/concentrated ammonia = 170/30/2)].

b) While stirring at from 5 to 10°, 0.95 g (20 mmol) of a sodium hydride suspension (50 % in oil) is added in portions to a solution of 3.4 g (20 mmol) of 2-(n-butyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazole in 50 ml of N,N-dimethylformamide. The mixture is then stirred for 1 hour at room temperature and then a solution of 5.6 g (10 mmol) of 2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl bromide in 20 ml of N,N-dimethylformamide is added. The reaction mixture is stirred for from 18 to 24 hours at an internal temperature of 20°, and then neutralised with acetic acid and, after the solvent has been evaporated off, partitioned between ethyl acetate and water. Concentration of the organic phase by evaporation yields 2-(n-butyl)-4,4-dimethyl-5-oxo-1-[2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole which is used further in its crude form.

Example 3: A solution of 2.4 g (6 mmol) of 2-(n-butyl)-3-(2'-cyanobiphenyl-4-ylmethyl)-4-oxo-1,3-diazaspiro[4.5]dec-1-ene and 3.6 g (10.8 mmol) of tributyltin azide in 50 ml of o-xylene is heated under reflux for 36 hours. Working up analogously to Example 1 using 50 ml of 1N potassium hydroxide solution yields an oil, from which, after the addition of a small amount of ethyl acetate, 2-(n-butyl)-4-oxo-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,3-diazaspiro[4.5]dec-1-ene [m.p.: 145-153° (sintering from 112°)] crystallises out.

The starting material can be prepared, for example, as follows:
a) In the course of 15 minutes, while stirring at room temperature, 14.5 g (120 mmol) of pentanoyl chloride are added to a suspension of 14.3 g (100 mmol) of 1-amino-1-carboxy-cyclohexane and 26 g (200 mmol) of Hünig base in 400 ml of tetrahydrofuran. The mixture is stirred for from 20 to 25 hours, the solvent is evaporated off, 100 ml of water are added to the residue and the mixture is stirred for 1 hour. The crystalline residue is filtered off and dried in vacuo. The resulting crude 1-carboxy-1-pentanoylaminocyclo-hexane has a melting point of 148-154° and can be processed further without further purification.

b) A mixture of 4.55 g (20 mmol) of 1-carboxy-1-pentanoylamino-cyclohexane, 3.45 g (30 mmol) of N-hydroxysuccinimide, 4.74 g (23 mmol) of N,N'-dicyclohexylcarbodiimide and 50 ml of N,N-dimethylformamide is stirred for 20 minutes at room temperature. A solution of 4.2 g (20 mmol) of 4-aminomethyl-2'-cyanobiphenyl in 10 ml of N,N-dimethylformamide is added to the resulting suspension and the mixture is stirred for 24 hours. Working up analogously to Example 1b) yields 1-(2'-cyanobiphenyl-4-ylmethyl-aminocarbonyl)-1-pentanoylaminocyclohexane, which gradually solidifies to form crystals and can be processed further in its crude form. A sample recrystallised from ethyl acetate has a melting point of 135-137°.

c) A mixture of 5.9 g (14 mmol) of crude 1-(2'-cyanobiphenyl-4-ylmethylamino-carbonyl)-1-pentanoylaminocyclohexane, 2.8 g (14 mmol) of p-toluenesulfonic acid monohydrate and 150 ml of xylene mixture is heated under reflux using a water separator. After 3 hours the water separator is replaced by a descending condenser and 50 ml of xylene are distilled off. The remaining solvent is distilled off in vacuo (approximately 1 mm Hg). The residue is partitioned between 20 ml of 2N sodium hydroxide solution and 200 ml of ethyl acetate. The residue obtained when the ethyl acetate has been evaporated

off is subjected to flash chromatography on silica gel with hexane/ethyl acetate (7/2). The product-containing fractions (R_f = 0.12) are combined and concentrated by evaporation, yielding 2-(n-butyl)-3-(2'-cyanobiphenyl-4-ylmethyl)-4-oxo-1,3-diazaspiro[4.5]dec-1-ene in the form of a pale brown oil.

Example 4: A solution of 0.59 g (1.6 mmol) of 1-(2'-cyanobiphenyl-4-ylmethyl)-4,4-diethyl-5-oxo-2-(n-propyl)-4,5-dihydro-1H-imidazole and 0.7 g (2.1 mmol) of tributyltin azide in 20 ml of xylene mixture is heated under reflux for 48 hours, a further 0.3 g of tributyltin azide being added after 18 hours. Working up analogously to Example 1 using 15 ml of 2N potassium hydroxide solution and purification by flash chromatography yield 4,4-diethyl-5-oxo-2-(n-propyl)-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole in the form of a colourless amorphous solid [R_f = 0.42 (toluene/isopropanol/glacial acetic acid = 170/30/2)].

The starting material can be prepared, for example, as follows:
a) Analogously to Example 3a) there is obtained from 2-amino-2-ethylbutanoic acid and butanoyl chloride 2-butanoylamino-2-ethylbutanoic acid [m.p.: 161-162° (from water)].

b) While stirring, 2.6 g (12.5 mmol) of N,N'-dicyclohexylcarbodiimide are added to a solution of 2.15 g (10.7 mmol) of 2-butanoylamino-2-ethylbutanoic acid and 2.0 g (16.7 mmol) of N-hydroxysuccinimide in 50 ml of N,N-dimethylformamide. After 20 minutes, a solution of 2.4 g (11 mmol) of 4-aminomethyl-2'-cyanobiphenyl in 20 ml of N,N-dimethylformamide is added. The reaction mixture is stirred for from 20 to 24 hours and then worked up analogously to Example 1b) to yield 2-butanoylamino-2-ethylbutanoic acid N-(2'-cyanobiphenyl-4-ylmethyl)amide in the form of an oil [R_f = 0.35 (toluene/-isopropanol/concentrated ammonia = 170/30/2)], which can be processed further in its crude form.

c) 2.0 g (10.5 mmol) of p-toluenesulfonic acid monohydrate are added to a solution of 4.1 g (10.5 mmol) of 2-butanoylamino-2-ethylbutanoic acid N-(2'-cyanobiphenyl-4-ylmethyl)amide in 100 ml of xylene mixture, and the reaction mixture is heated under reflux using a water separator. After 6 hours the reaction mixture is worked up analogously to Example 3c) and the crude product is subjected to flash chromatography on 400 g of silica gel (toluene/methanol = 19/1). The product-containing fractions (R_f = 0.15) are combined and concentrated by evaporation, yielding 1-(2'-cyanobiphenyl-4-ylmethyl)-4,4-diethyl-5-oxo-2-(n-propyl)-4,5-dihydro-1H-imidazole in the form of a

yellowish oil.

Example 5: A solution of 0.33 g (1.0 mmol) of 5-(n-butyl)-3-oxo-4-(2'-cyanobiphenyl-4-ylmethyl)-2,3-dihydro-4H-1,2,4-triazole and 0.43 g (1.3 mmol) of tributyltin azide in 5 ml of o-xylene is heated under reflux for 28 hours. The reaction mixture is diluted with 10 ml of toluene, 4 ml of 1N sodium hydroxide solution are added and the reaction mixture is stirred for 2 hours. The aqueous phase is separated off, adjusted to pH 3 to 4 with acetic acid and extracted with ethyl acetate. After drying and evaporating off the solvent an oil is obtained from which 5-(n-butyl)-3-oxo-4-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-2,3-dihydro-4H-1,2,4-triazole gradually crystallises out [m.p.: 213-215° (from acetonitrile)].

The starting material can be prepared, for example, as follows:
a) A solution of 4.16 g (20 mmol) of 4-aminomethyl-2'-cyanobiphenyl and 7.0 ml of 1,1,1-trimethoxypentane in 40 ml of toluene is heated under reflux for from 10 to 12 hours. Concentration by evaporation in vacuo yields 1-[N-(2'-cyanobiphenyl-4-ylmethyl)imino]-1-methoxypentane in the form of an oil that is processed further in its crude form.

b) 1.3 g (approx. 4 mmol) of crude 1-[N-(2'-cyanobiphenyl4-ylmethyl)imino]-1-methoxy-pentane and 0.5 g (5 mmol) of ethoxycarbonylhydrazine are heated under reflux for 20 hours in 10 ml of toluene. Washing of the cooled solution, first with 5 ml of aqueous 1N methanesulfonic acid solution and then with saturated sodium hydrogen carbonate solution, and concentration of the organic phase by evaporation yield an oil from which 5-(n-butyl)-3-oxo-4-(2'-cyanobiphenyl-4-ylmethyl)-2,3-dihydro-4H-1,2,4-triazole gradually crystallises out [m.p.: 134-135° (from acetonitrile)].

Example 6: A solution of 3.7 g (10.3 mmol) of 2-(n-butyl)-1-(2'-cyanobiphenyl-4-ylmethyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazole and 4.4 g (13 mmol) of tributyltin azide in 40 ml of o-xylene is heated under reflux for 26 hours. Working up analogously to Example 1 yields a crude product from which there is obtained by recrystallisation from ethyl acetate 2-(n-butyl)-4,4-dimethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole having a melting point of 180-181°.

The starting material can be prepared, for example, as follows:
A solution of 7.5 g (20 mmol) of 2-methyl-2-pentanoylaminopropionic acid N-(2'-cyano-

biphenyl-4-ylmethyl)amide and 4.0 g (20 mmol) of p-toluenesulfonic acid in 200 ml of toluene is heated under reflux for 12 hours using a water separator. The reaction mixture is then stirred with 20 ml of 2N sodium hydroxide solution and the toluene phase is separated off, washed with water, dried and concentrated by evaporation in vacuo. The resulting crude product is subjected to flash chromatography on silica gel (toluene/-methanol = 19/1). The product-containing fractions ($R_f = 0.22$) are combined and concentrated by evaporation, yielding 2-(n-butyl)-1-(2'-cyanobiphenyl-4-ylmethyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1H-imidazole in the form of a colourless oil.

Example 7: At room temperature, 4.4 ml of a solution of hydrogen chloride in ethanol (10N) are added to a solution of 2-(n-butyl)-4,4-dimethyl-6-oxo-1-[2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydropyrimidine (2.90 g, 4.4 mmol) in 10 ml of CH_2Cl_2. After 30 minutes the reaction mixture is concentrated by evaporation in vacuo, toluene is added to the residue and the mixture is again concentrated by evaporation in vacuo. After the addition of ethyl acetate, the mixture is filtered and the filter cake is recrystallised from acetonitrile. After drying in vacuo at 100° there remains 2-(n-butyl)-4,4-dimethyl-6-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydropyrimidine hydrochloride [m.p.: 245° (decomposition)].

The starting material can be prepared, for example, as follows:
a) 3,3-dimethylacrylic acid ethyl ester (5.06 ml, 36.44 mmol) and valeric amidine (3.65 g, 36.44 mmol) are stirred at room temperature for 12 hours. After concentration by evaporation in vacuo, the residue is dissolved in 20 ml of ethanol and 6 ml of a solution of hydrogen chloride in ethanol (10N) are added to the solution. The precipitate is filtered off and the filter cake is recrystallised from ethanol, yielding 2-(n-butyl)-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrimidine hydrochloride (m.p.: 215-218°).

b) NaH (80 % in white oil; 0.36 g, 11.9 mmol) is added to a solution of 2-(n-butyl)-4,4-dimethyl-6-oxo-1,4,5,6-tetrahydropyrimidine hydrochloride (1.30 g, 5.94 mmol) in 20 ml of N,N-dimethylformamide. The suspension is stirred for 1 hour at room temperature, and then a solution of 2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl bromide (3.31 g, 5.94 mmol) in 25 ml of N,N-dimethylformamide is added dropwise and the reaction mixture is stirred for 12 hours at room temperature. After concentration by evaporation in vacuo the residue is partitioned between water and ethyl acetate and the organic phase is dried over Na_2SO_4 and concentrated by evaporation in vacuo. Flash chromatography (silica gel 60, 40-63 µm, $CH_2Cl_2/CH_3OH = 95/5$) yields 2-(n-butyl)-4,4-

dimethyl-6-oxo-1-[2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydropyrimidine which is further processed directly.

Example 8: Starting from 2-(n-butyl)-5,5-dimethyl-6-oxo-1-[2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydropyrimidine, there is obtained in the manner described in Example 7 2-(n-butyl)-5,5-dimethyl-6-oxo-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-1,4,5,6-tetrahydropyrimidine hydrochloride [m.p.: 187-191° (decomposition)].

The starting material can be obtained, for example, as follows:
a) 3-amino-2,2-dimethylpropionic acid ethyl ester (1.45 g, 10 mmol) and valeric amidine (1.0 g, 10 mmol) are stirred under reflux for 6 hours. After concentration by evaporation, the residue is partitioned between water and ethyl acetate and the organic phase is dried over Na_2SO_4 and concentrated by evaporation in vacuo. Flash chromatography (silica gel 60, 40-63 µm, ethyl acetate) yields 2-(n-butyl)-5,5-dimethyl-6-oxo-1,4,5,6-tetrahydro-pyrimidine which is converted into the hydrochloride by treatment with a solution of hydrogen chloride in ether and processed further directly in that form.

b) Alkylation of 2-(n-butyl)-5,5-dimethyl-6-oxo-1,4,5,6-tetrahydropyrimidine hydrochloride with 2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-ylmethyl bromide, followed by flash chromatography in the manner described in Example 7b), yields 2-(n-butyl)-5,5-dimethyl-6-oxo-1-[2'-(1-triphenylmethyl-1H-tetrazol-5-yl)biphenyl-4-yl-methyl]-1,4,5,6-tetrahydropyrimidine, which is processed further directly.

Example 9: A solution of 5.0 g (13 mmol) of 2-(n-butyl)-3-(2'-cyanobiphenyl-4-ylmethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-ene and 5.6 g (16.9 mmol) of tributyltin azide in 100 ml of o-xylene is heated under reflux for 40 hours. Working up analogously to Example 1 yields a partially crystalline crude product the crystalline portion of which, after recrystallisation from isopropanol, yields pure 2-(n-butyl)-4-oxo-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,3-diazaspiro[4.4]non-1-ene (m.p.: 181-183°).

The starting material can be prepared, for example, as follows:
a) 1-amino-1-benzyloxycarbonylcyclopentane is reacted with pentanoyl chloride to form 1-benzyloxycarbonyl-1-pentanoylaminocyclopentane (m.p.: 46-48°).

b) Catalytic debenzylation of 1-benzyloxycarbonyl-1-pentanoylaminocyclopentane by

means of Pd/C (10%) in methanol yields 1-carboxy-1-pentanoylaminocyclopentane (m.p.: 192-194°).

c) Analogously to Example 3b) there is obtained using 4.26 g (20 mmol) of 1-carboxy-1-pentanoylaminocyclopentane 1-(2'-cyanobiphenyl-4-ylmethylaminocarbonyl)-1-pentanoylaminocyclopentane [m.p.: 140-142° (from ethyl acetate)].

d) A solution of 7.3 g (18 mmol) of 1-(2'-cyanobiphenyl-4-ylmethylaminocarbonyl)-1-pentanoylaminocyclopentane and 3.5 g (18.4 mmol) of p-toluenesulfonic acid-monohydrate in 150 ml of toluene is heated under reflux for 20 hours using a water separator. Working up analogously to Example 3c) yields crude 2-(n-butyl)-3-(2'-cyanobiphenyl-4-ylmethyl)-4-oxo-1,3-diazaspiro[4.4]non-1-ene in the form of a yellowish oil [R_f = 0.61 (toluene/isopropanol/concentrated ammonia = 170/30/2)], which is reacted further without additional purification.

Example 10: A solution of 0.95 g (2.4 mmol) of 2-(n-butyl)-1-(2'-cyanobiphenyl-4-ylmethyl)-4,4-diethyl-5-oxo-4,5-dihydro-1H-imidazole and 1.22 g (3.6 mmol) of tributyltin azide in 10 ml of o-xylene is heated under reflux for 48 hours. Working up analogously to Example 1 yields a crude product from which there is obtained by recrystallisation from ethyl acetate/diethyl ether 2-(n-butyl)-4,4-diethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole (m.p.: 120-121°).

The starting material can be prepared, for example, as follows:
a) Analogously to Example 3a) there is obtained from 2-amino-2-ethylbutanoic acid and pentanoyl chloride 2-ethyl-2-pentanoylaminobutanoic acid in the form of an oil [R_f = 0.27 (toluene/methanol = 4/1)], which is reacted further without additional purification.

b) Analogously to Example 4b) there is obtained from 2-ethyl-2-pentanoylaminobutanoic acid 2-ethyl-2-pentanoylaminobutanoic acid N-(2'-cyanobiphenyl-4-ylmethyl)amide in the form of an oil [R_f = 0.46 (toluene/isopropanol/concentrated ammonia = 170/30/2)], which is purified by means of flash chromatography (toluene/methanol = 40/1).

c) A solution of 1.0 g (2.46 mmol) of 2-ethyl-2-pentanoylaminobutanoic acid N-(2'-cyanobiphenyl-4-ylmethyl)amide and 0.52 g (2.7 mmol) of p-toluenesulfonic acid monohydrate in 50 ml of o-xylene is heated under reflux for 48 hours using a water separator. The cooled reaction mixture is diluted with 50 ml of ethyl acetate and rendered alkaline

with 10 ml of 2N sodium hydroxide solution. The organic phase is washed in succession with water and brine, dried and concentrated by evaporation in vacuo. The 2-(n-butyl)-1-(2'-cyanobiphenyl-4-ylmethyl)-4,4-diethyl-5-oxo-4,5-dihydro-1H-imidazole obtained in the form of an oil [R_f = 0.45 (toluene/methanol = 4/1)] is reacted further without additional purification.

Example 11: The following compounds can be prepared in a manner analogous to that described in any one of the preceding Examples:

1. 2-(n-butyl)-6-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydropyrimidine,
2. 2-(n-butyl)-6-oxo-4,4,5,5-tetramethyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydropyrimidine,
3. 2-(n-butyl)-4-isopropyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole,
4. 1,3-di-(n-butyl)-5-oxo-4-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,5-dihydro-4H-1,2,4-triazole,
5. 4,4-dimethyl-5-oxo-2-(n-propyl)-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole,
6. 4,4-dimethyl-5-oxo-2-(n-pentyl)-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole,
7. 2-(n-butyl)-4-isopropyl-4-methyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole,
8. 3-(n-butyl)-1-methyl-5-oxo-4-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,5-dihydro-4H-1,2,4-triazole,
9. 2-(n-butyl)-4-methyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole,
10. 2-(n-butyl)-4-ethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole and
11. 2-(n-butyl)-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole,

in each case in free form or in the form of a salt, for example in the form of the hydrochloride.

Example 12: Tablets, each comprising 50 mg of active ingredient, for example 2-(n-butyl)-4,4-dimethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole, can be prepared as follows:

Composition (for 10 000 tablets):		
active ingredient		500.0 g
lactose		500.0 g
potato starch		352.0 g
gelatin	8.0 g	
talcum	60.0 g	
magnesium stearate		10.0 g
silica (highly dispersed)	20.0 g	
ethanol		q.s.

The active ingredient is mixed with the lactose and 292 g of the potato starch, and the mixture is moistened with an alcoholic solution of the gelatin and granulated through a sieve. After drying, the remaining potato starch, the talcum, the magnesium stearate and the highly dispersed silica are mixed in and the mixture is compressed to form tablets which each weigh 145.0 mg and comprise 50.0 mg of active ingredient, and which may, if desired, be provided with breaking notches for finer adaptation of the dose.

Example 13: Film-coated tablets, each comprising 100 mg of active ingredient, for example 2-(n-butyl)-4,4-dimethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole, can be prepared as follows:

Composition (for 1000 tablets):		
active ingredient	100.00 g	
lactose		100.00 g
corn starch	70.00 g	
talcum	8.50 g	
calcium stearate	1.50 g	
hydroxypropylmethylcellulose		2.36 g
shellac	0.64 g	
water	q.s.	
dichloromethane	q.s.	

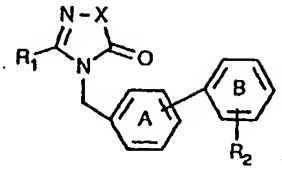
The active ingredient, the lactose and 40 g of the corn starch are mixed, and the mixture is moistened with a paste, prepared from 15 g of the corn starch and water (with heating), and granulated. The granules are dried, the remaining corn starch, the talcum and the

calcium stearate are added and mixed with the granules. The mixture is compressed to form tablets (weight: 280 mg), which are film-coated with a solution of the hydroxypropylmethylcellulose and the shellac in dichloromethane (final weight of the film-coated tablet: 283 mg).

Example 14: In a manner analogous to that described in Examples 12 and 13, it is also possible to prepare tablets and film-coated tablets comprising a different compound I or a tautomer of a compound I or a pharmaceutically acceptable salt of a compound I or of a tautomer of a compound I, for example in accordance with any one of Examples 1 to 11.

What is claimed is:

1. A compound of the formula



(I),

wherein X is the group of the formula $-C(R_3)R_4-[C(R_5)R_6]_p-[C(R_7)R_8]_q-$ (Ia) or the group of the formula $-N(R_9)-$ (Ib), R_1 is unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of hydroxy and halogen; cycloalkyl, cycloalkenyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, R_2 is carboxy, 1H-tetrazol-5-yl, SO_3H, PO_2H_2, PO_3H_2 or haloalkanesulfonylamino, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen, unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of halogen, free or etherified hydroxy, free or esterified or amidated carboxy and unsubstituted or substituted amino; free or esterified or amidated carboxy, cycloalkyl, cycloalkenyl, an aliphatic hydrocarbon radical interrupted by O, or an aromatic radical, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is a divalent aliphatic hydrocarbon radical and the variables of the other two pairs, independently of one another, are as defined above, R_9 is hydrogen or unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of free or etherified hydroxy and free or esterified or amidated carboxy, the indices p and q, independently of one another, are 0 or 1 and the rings A and B, independently of one another, are unsubstituted or substituted, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

2. A compound of formula I according to claim 1, wherein X is the group Ia or the group Ib, R_1 is unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of hydroxy and halogen; cycloalkyl, cycloalkenyl, phenyl-lower alkyl, phenyl-lower alkenyl or phenyl-lower alkynyl, R_2 is carboxy, 1H-tetrazol-5-yl, SO_3H, PO_2H_2, PO_3H_2 or

haloalkanesulfonylamino, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen, unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of halogen, hydroxy, lower alkoxy, lower alkenyloxy, carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or to lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is di-substituted by lower alkylene or by lower alkyleneoxy-lower alkylene; amino and amino that is mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene; or are carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or to lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is di-substituted by lower alkylene or by lower alkyleneoxy-lower alkylene; cycloalkyl, cycloalkenyl, lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, lower alkenyloxy-lower alkyl, -lower alkenyl or -lower alkynyl, phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is lower alkylene or lower alkenylene, and the variables of the other two pairs, independently of one another, are as defined immediately above, R_9 is hydrogen or unsubstituted or mono- or poly-substituted lower alkyl, lower alkenyl or lower alkynyl, it being possible for the substituents to be selected from the group consisting of lower alkoxy, lower alkenyloxy, carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or to lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl, and carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene, the indices p and q, independently of one another, are 0 or 1, and the rings A and B, independently of one another, are unsubstituted or mono- or poly-substituted, it being

possible for the substituents to be selected from the group consisting of halogen, hydroxy, lower alkoxy, lower alkenyloxy, amino, amino mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene; carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl, lower alkenyl, lower alkynyl or to lower alkoxy-lower alkyl, -lower alkenyl or -lower alkynyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl, lower alkenyl, lower alkynyl, hydroxy-lower alkyl, lower alkoxy-lower alkyl and phenyl-lower alkyl, -lower alkenyl or -lower alkynyl, or is disubstituted by lower alkylene or by lower alkyleneoxy-lower alkylene; and lower alkyl, lower alkenyl, lower alkynyl, lower alkoxy-lower alkyl, -lower alkenyl and -lower alkynyl, lower alkenyloxy-lower alkyl, -lower alkenyl and -lower alkynyl and trifluoromethyl, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

3. A compound of formula I according to claim 1, wherein X is the group Ia or the group Ib, R_1 is lower alkyl, lower alkenyl, lower alkynyl, cycloalkyl or phenyl-lower alkyl, R_2 is carboxy, 1H-tetrazol-5-yl, SO_3H, PO_2H_2, PO_3H_2 or haloalkanesulfonylamino, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different lower alkyl substituents; cycloalkyl, lower alkoxy-lower alkyl, phenyl, naphthyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, furyl, thienyl or pyridyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is lower alkylene or lower alkenylene and the variables of the other two pairs, independently of one another, are as defined immediately above, R_9 is hydrogen, lower alkyl, lower alkenyl or lower alkynyl, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B, independently of one another, are unsubstituted or mono- or poly-substituted, it being possible for the substituents to be selected from the group consisting of halogen, hydroxy, lower alkoxy, amino, amino mono- or di-substituted by identical or different substituents selected from lower alkyl and phenyl-lower alkyl, carboxy, carboxy esterified by an alcohol the alcoholic hydroxy function of which is bonded to lower alkyl; carbamoyl the amino group of which is unsubstituted or mono- or di-substituted by identical or different substituents selected from lower alkyl and phenyl-lower alkyl, or is disubstituted by lower

alkylene or by lower alkyleneoxy-lower alkylene; and lower alkyl and trifluoromethyl, and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

4. A compound of formula I according to claim 1, wherein X is the group Ia or the group Ib, R_1 is C_1-C_4alkyl, R_2 is carboxy or 1H-tetrazol-5-yl, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen or C_1-C_4alkyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is C_2-C_5alkylene, and the variables of the other two pairs, independently of one another, are as defined immediately above, R_9 is hydrogen or C_1-C_4alkyl, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B are unsubstituted and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

5. A compound of formula I according to claim 1, wherein X is the group Ia or the group Ib, R_1 is C_1-C_4alkyl, R_2 is 1H-tetrazol-5-yl, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen or C_1-C_4alkyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is C_2-C_5alkylene and the variables of the other two pairs are hydrogen, R_9 is hydrogen, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B are unsubstituted and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt.

6. A compound of formula I according to claim 1, wherein X is the group Ia, R_1 is C_1-C_4alkyl, R_2 is 1H-tetrazol-5-yl, either R_3, R_4, R_5, R_6, R_7 and R_8, independently of one another, are hydrogen or C_1-C_4alkyl, or one of the three pairs of variables R_3/R_4, R_5/R_6 and R_7/R_8 is C_2-C_5alkylene and the variables of the other two pairs are hydrogen, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B are unsubstituted and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, in free form or in the form of a salt.

7. A compound of formula I according to claim 1, wherein X is the group Ia, R_1 is C_1-C_4alkyl, R_2 is 1H-tetrazol-5-yl, R_3, R_4, R_5, R_6, R_7 and R_8, independently of one

another, are hydrogen or C_1-C_4alkyl, either the indices p and q are 0 or one of the indices p and q is 0 and the other of the indices p and q is 1, the rings A and B are unsubstituted and the ring B is bonded in the 4-position of the ring A and R_2 is bonded in a 2-position of the ring B, in free form or in the form of a salt.

8. 2-(n-butyl)-4,4-dimethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

9. 2-(n-butyl)-4-oxo-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,3-diazaspiro[4.5]-dec-1-ene or a salt thereof.

10. 4,4-diethyl-5-oxo-2-(n-propyl)-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

11. 5-(n-butyl)-3-oxo-4-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-2,3-dihydro-4H-1,2,4-triazole or a tautomer and/or a salt thereof.

12. 2-(n-butyl)-4,4-dimethyl-6-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydro-pyrimidine or a salt thereof.

13. 2-(n-butyl)-5,5-dimethyl-6-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydro-pyrimidine or a salt thereof.

14. 2-(n-butyl)-6-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydro-pyrimidine or a salt thereof.

15. 2-(n-butyl)-6-oxo-4,4,5,5-tetramethyl-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,4,5,6-tetrahydro-pyrimidine or a salt thereof.

16. 2-(n-butyl)-4,4-diethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

17. 2-(n-butyl)-4-oxo-3-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,3-diazaspiro[4.4]-non-1-ene or a salt thereof.

18. 2-(n-butyl)-4-isopropyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-

4,5-dihydro-1H-imidazole or a salt thereof.

19. 1,3-di-(n-butyl)-5-oxo-4-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,5-dihydro-4H-1,2,4-triazole or a salt thereof.

20. 4,4-dimethyl-5-oxo-2-(n-propyl)-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

21. 4,4-dimethyl-5-oxo-2-(n-pentyl)-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

22. 2-(n-butyl)-4-isopropyl-4-methyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

23. 3-(n-butyl)-1-methyl-5-oxo-4-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-1,5-dihydro-4H-1,2,4-triazole or a salt thereof.

24. 2-(n-butyl)-4-methyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

25. 2-(n-butyl)-4-ethyl-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

26. 2-(n-butyl)-5-oxo-1-[2'-(1H-tetrazol-5-yl)biphenyl-4-ylmethyl]-4,5-dihydro-1H-imidazole or a salt thereof.

27. A compound according to any one of claims 1 to 26 or, if appropriate, a tautomer thereof, in each case in free form or in the form of a pharmaceutically acceptable salt, for use in a method for the therapeutic treatment of the human or animal body.

28. A compound according to any one of claims 1 to 27 or, if appropriate, a tautomer thereof, in each case in free form or in the form of a pharmaceutically acceptable salt, for use as an antihypertensive drug.

29. A pharmaceutical composition comprising as active ingredient a compound according to any one of claims 1 to 28 or, if appropriate, a tautomer thereof, in each case in free form

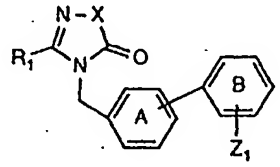
--

or in the form of a pharmaceutically acceptable salt, if desired together with customary pharmaceutical excipients.

30. An antihypertensively active pharmaceutical composition according to claim 29 wherein an antihypertensively active compound is selected.

31. A process for the preparation of a compound of formula I according to any one of claims 1 to 26 or, if appropriate, a tautomer thereof, in each case in free form or in the form of a salt, which comprises

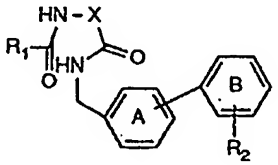
a) in a compound of the formula



(II),

wherein Z_1 is a radical that can be converted into R_2, or in a salt thereof, converting Z_1 into R_2, or

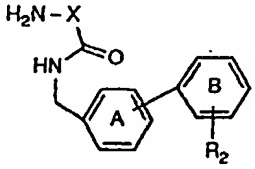
b) cyclising a compound of the formula



(III),

or a salt thereof, or

c) reacting a compound of the formula



(IV),

or a salt thereof, with a compound of the formula

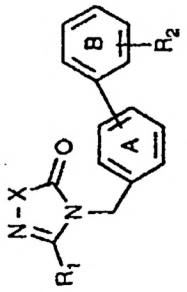
$$R_1\text{-}C(Z_2)(Z_3)Z_4 \qquad (V),$$

wherein either Z_2 and Z_3 together are unmodified or functionally modified oxo and Z_4 is a nucleofugal leaving group, or Z_2, Z_3 and Z_4, independently of one another, are a nucleofugal leaving group, and in each case, if desired, converting a compound I obtainable in accordance with the process or in another manner, or a tautomer thereof, in each case in free form or in the form of a salt, into a different compound I or a tautomer thereof, separating a mixture of isomers obtainable in accordance with the process and isolating the desired isomer and/or converting a free compound I obtainable in accordance with the process, or a tautomer thereof, into a salt, or converting a salt of a compound I obtainable in accordance with the process, or of a tautomer thereof, into the free compound I or a tautomer thereof or into a different salt.

32. A method for the treatment of high blood pressure and/or cardiac insufficiency, which comprises administering a compound according to any one of claims 1 to 28 or, if appropriate, a tautomer thereof, in each case in free form or in the form of a pharmaceutically acceptable salt, or a pharmaceutical composition according to claim 29 or claim 30.

33. The use of a compound according to any one of claims 1 to 28 or, if appropriate, of a tautomer thereof, in each case in free form or in the form of a pharmaceutically acceptable salt, for the preparation of a pharmaceutical composition.

Fetherstonhaugh & Co.,
Ottawa, Canada
Patent Agents


B
R2
A
O
N-X
N
R1